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Life as a numerator: Putting the person in personal genomics

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1. Introduction

While the science of human genomics is often focused on odds and probability, most of us do not experience risk that way.

I am a carrier of a mutation in *ABCC6*, as is my husband. Rather than experiencing the odds we would have children with the autosomal recessive condition pseudoxanthoma elasticum (25% each pregnancy) as an abstraction, our reality is having two of two children affected by PXE: our experience is 100%. Twice.

PXE affects 1 in 50,000 people. Our kids are the numerators. In 1994, when PXE was discovered in our then-very-young children, we felt not only overwhelmed by the prospect of taking care of them and anxious about the uncertainty of their futures, but isolated by the rare nature of their condition. Genetics? We didn't want to talk about it then and even if we did, we didn't have anyone with whom we *could* talk about it.

Today? Not so much. We—and thousands of others in similar circumstances—are bombarded with information from sequencing centers, clinics, research studies, and direct-to-consumer sites. And, spam fatigue notwithstanding, that's mostly to the good. Genetic disease is a long-tail problem that can only be solved if crowdsourcing rises to the occasion, that is, if families like mine and others contributing to and discussed in this issue are not alone. Precision medicine, biomedical research, and human health writ large all stand to benefit if the masses get involved. Indeed, I would argue that crowdsourcing is our only hope. Here I describe ways in which this is already happening and a vision for a future where it is standard practice.

2. Life on Mars

When our two children were diagnosed with PXE, it felt like we landed on Mars and were being chased by the grim reaper. Fear ripped through us, and no one was speaking words we could understand. This was not just because we could not hear through our fear, but because the world of biomedical research and disease characterization has an incredibly esoteric and complex vocabulary. Even the sentence structures were complicated — all passive voice and past tense. It was as though the language—and by extension, our family—was not alive anymore.

As if it weren't terrifying enough to enter the stigma-ridden land of The Diagnosed, we immediately discovered an astonishing fact: *scientists were not sharing*. A few days after our kids' diagnoses, scientists from Harvard came to draw blood from us to use in the search for the causative gene. Two days after that, a separate group of scientists called from the Mt. Sinai Hospital in New York and asked for blood to work on PXE gene discovery. When we asked the second set of researchers to ask the first set for blood (and perhaps even collaborate), they expressed amazement that we would ask such a thing! We were struck by how the culture of science, particularly in biomedical research, had so colored the researchers' perspectives that they found our request preposterous. We felt both horrified and hopelessly naive.

But this was only our first foray into a world that left us surprised over and over: a world alien and offensive to us in our need. It seemed that publishing, getting tenure and getting promoted were more important than discovering what was causing PXE. We quickly got over our expectations for a rapid treatment, let alone a cure. What we couldn't get over were the lack of sharing and the intense competition among scientists. Twenty years on we're still not over it.

In 1995 we built a biobank and stored the samples at a major medical center. That was fine until we wanted to share those precious samples beyond that particular university. After notifying the researchers there that we were on our way to the laboratory to take one of 20 stored DNA aliquots per person, each of which we had deposited there ourselves, we arrived to find a lock on the freezer. Many months of arguing ensued, and we finally called the vice president of the medical center. He ordered the release of our samples. We informed the institution that we would be moving the entire collection of hundreds of samples. On the day we arrived to do that, we found the samples on a cart in the hallway — thawed and warm. We also saw that we were missing several aliquots per person. We took our room-temperature samples across town to freezer space we were renting. And then we took our anger and disappointment and channeled them into changing the system.

A few years later, I spent months negotiating the opportunity to do a natural history study of PXE at the National Institutes of Health. I offered to support the salary of a clinician researcher to do the study. Two glaring disconnects emerged. The first related to the study protocol. At this point, I had collected 900 fields of data on 4000 people living with PXE and knew something about its signs, symptoms and progression. But the investigators were adamant that they would focus on measuring phenotypic characteristics that had no correlation to PXE! They discounted our experience and our copious data. Second, they refused to let me be part of the study team. The "offer" was for me to sit in the back of the room; someone even made a joke that I could carry one of the researcher's briefcases. Their excuse for excluding me was that I was not credentialed in biomedical research. Nevermind that I had the equivalent of a PhD in PXE.

These experiences, and dozens of others, fueled a passion in me to lead an organization that was focused on the very people who need

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their suffering alleviated—one that was less concerned with academic status and more focused on improving the lives of patients and families. I became interested in practical tools that could be applied to any disease or condition, that could help break down silos and enable sharing despite systems and bureaucrats that were and are often obstacles to the outcomes we seek.

Even more critical to me is trying to change the fundamental misalignments embedded in health care and biomedical research. When the President of the United States embraces the rhetoric of patient- and participant-centric research, we can safely say it has reached new heights. Indeed, it was music to my ears to sit in the East Wing in early 2015 and hear Barack Obama say "… I'm proud we have so many patients' rights advocates with us here today. They're not going to be on the sidelines. It's not going to be an afterthought. They'll help us design this initiative from the ground up, making sure that we harness new technologies and opportunities in a responsible way" (Anon., 2015).

As I write this nearly a year later, however, we have yet to see the deep and essential fundamental shift. We are behaving as though we believe that engagement and partnership have value, but we are still not able to articulate that value, and we are not able to tell the truth about the incentives that drive the biomedical research system. I sit in discussions about "patient-centricity" and wonder why the way we keep score remains rooted in tallies of publications and grant monies. I understand that for systems to change to realize beneficial health outcomes requires a long timeline. But I do not apologize for my impatience. Academia, regulators and even many in pharma seem to accept the ideas that: 1) developing drugs requires a decade; and 2) patients are passive data points in this process, i.e., they are to be collected, not consulted.

3. Strange attractors

In most of my encounters with the biomedical research system and its recent lust for big data – especially genotype and phenotype data – I've found that that those who champion "engagement" often see it as a useful euphemism for recruitment. At one level I understand this: I do not advocate for engagement for engagement's sake. But neither do I reduce it to a top-down call for increased sample size at all costs.

I think that this new intense interest in engagement, participation, and partnership is what chaos theorists David Ruelle and Floris Takens would call a "strange attractor" (Ruelle and Takens, 1971). The definition describes "basins of attraction within the system that lure the system into a new pattern of activity." Engagement and participation, I hope and expect, will recenter the system and create authentic partnerships. Individuals, families and communities will take their rightful place as co-designers of new ways of engaging with their health.

In this regard, I am all in on an experiment. Together with Private Access, an innovative technology company, Genetic Alliance has built the Platform for Engaging Everyone Responsibly (PEER). It shifts the center of attention away from institutions, researchers, and even advocacy organizations, and toward individuals. Using PEER, each individual makes choices about data sharing, privacy, and access in a granular and dynamic way. It is our firm belief (and we have invited researchers to study this hypothesis) that if people make these choices for themselves, they will drive the market. They will aggregate themselves not in disease silos, but in pathways, phenotypes and symptoms that they strongly feel need attention and to which they are prepared to commit.

How does PEER work? In one example, we engaged with five sickle cell advocacy organizations and were able to learn from individuals living with sickle cell what mattered to them, and to deliver this information, along with patients' associated socioeconomic data, to the Food and Drug Administration for its Patient-Focused Drug Development program. We therefore extended the reach of the FDA's program to individuals who couldn't travel to metro DC to attend a hearing, or who were not able to post to the docket (the special web-based system that the government uses to catalog public comments).

In another example that is ongoing, ten disease advocacy organizations are working together in a boundary-free way to use the health information they collect across 15 diseases encompassing seemingly unrelated common (e.g., hepatitis, breast cancer) and rare (e.g., dyskeratosis congenita, Joubert syndrome) conditions. As a part of PCORnet, the national clinical research network being created by the Patient Centered Outcomes Research Institute (PCORI), these organizations are working to define research priorities and advance them together. This example is just one of 20 Patient-Powered Research Networks (PPRN) in PCORI that seek to run dozens of experiments on what constitutes true participant-centric research, how to build a network that will shift the current paradigm, and how to develop more robust strange attractors, all while measuring their impact on the current research and services system.

Plenty of obstacles and challenges to these sorts of approaches remain. Large-scale research on human beings is a young pursuit. And formal governance of it is even younger. Most of the same incentives that kept researchers from sharing samples and data in 1994 are still in place. And while patient- and participant-advocates are more frequently invited to discussions surrounding research initiatives, we are still routinely marginalized: we have a seat at the table but rarely do we get to have any meaningful say about what's on the menu or who should be invited to the meal. I hear rhetoric calling for "bridging to 'those' people" and "inviting them in." But to my ears those terms are harsh and grating: they perpetuate an "us" and a "them." We are all us and we are all them.

4. Street cred

The "us and them" frame is more than a linguistic peeve. In recent years, those of us who have been at this for a while have found our legitimacy called into question. There are those, even within the patient and participant advocacy movements, who now routinely discount what some of us do. Some claim that we are not 'true patients' because we have peer-reviewed papers, conduct research, lead large organizations and/or work to influence policy at multiple levels—we are "them." In ways that I find both saddening and ironic, it seems that our very efforts have somehow sowed distrust. We are suddenly written off as having Stockholm syndrome or not truly representing patients.

More than any slight from a researcher ever could, hearing this from fellow advocates hurts. I am still, first and foremost, mother to my two children who live with a genetic condition. I would much rather my family not live life as a numerator, but I—like all families coping with any of the thousands of serious health conditions, be they common or rare—have no choice. All we can do is fight.

Meanwhile, my daughter has succeeded me as the executive director of PXE International. She has doubled the organizational budget and doubled the number of affected individuals enrolled in two short years. Her mission, like mine, remains unchanged: it is not to have a scientific career or access to power, but to alleviate suffering—her own, her brother's, and the thousands like them.

When we have done that for the larger community of numerators, we will gladly shut off the lights and go home.

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